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Priorities in the Investigation of Human Health Hazards in the Plastics and Synthetic Rubber Industries

by Irving J. Selikoff*

Experiences in the past decade provide guidance in selecting priorities for investigation of health hazards in chemical industries. Pride of place should be given to the experience of large industrial populations, in part simply because large numbers of people are at risk and in part because such studies are more likely to give reliable answers. This recommendation has further strength when there is community exposure as well. Parenthetically, large populations provide opportunity to study multiple factor interaction; without this, toxic potential of a single agent may be obscured. Second, investigations should be mounted when there is reason for suspicion, as with particular chemical configurations, observed organ toxicity, animal carcinogenicity, unusual clinical experience ("signal" tumors). It may be added that when agents have already been used several decades, evaluation of human experience with them is now in order, if only to document absence of toxicity. The same recommendations hold for planned introduction of new agents or widened distribution of existing ones, until we have better information concerning validity of "pretesting" programs.

Major advances have been made in epidemiological methods for these investigations. These now allow us to successfully focus on small defined groups as well as to manage large populations.

The Paradox of Rehn

In 1895, Rehn reported three cases of cancer of the bladder among fuchsin dye workers (*1*). Additional cases of an association between aniline dye exposure and bladder tumors were identified during the next 15 years in Germany and Switzerland. An assumption was projected that the developing chemical industry, with its increasing number of synthetic chemicals new to the human environment, would bring with it a harvest of cancer. This prediction, in the next decades, seemed far from unreasonable when carcinogenicity of literally hundreds of chemicals in animal test studies was found (*2*).

Yet, by and large, the prophecy was not seen to be fulfilled in the first half of this century. Even until recently, chemically induced cancers in humans have been relatively few and restricted in type and number. β-Naphthylamine and benzidine bladder cancer, radium neoplasms, coal tar skin cancers, sinus and lung cancer with some nickel compounds seemed exceptions to the broad spectrum of human concern.

Thus, until recent years, we were faced with something of a paradox; Rehn and his contemporaries had shown that human cancer could result from chemical industry exposure, laboratory studies indicated that agents could be varied and numerous, yet human experience had not demonstrated this to be a major problem.

In recent years, the question has again been put before us in pressing terms. Do experiences with vinyl chloride, bischloromethyl ether, benzene, chromates, etc., demonstrate that the prophecies were really correct, merely premature? We do not yet know, but the question is an important one and must be now addressed.

Priorities

The problem is immense and resources for its consideration scant and limited. From a societal point of view, it is therefore advantageous to

* Mount Sinai School of Medicine of the City University of New York, New York, New York 10029.

consider priorities for the utilization of these scarce resources in personnel, facilities, support. Experiences in the past decade provide some guidance to how these might be considered (*3*), and, while they are largely related to U.S. circumstances, the world-wide growth of the plastics and synthetic rubber industry suggests they may have broader application as well (*4*).

Exposure of Large Industrial Populations

The experience of large groups of occupationally exposed workers should take pride of place in evaluative studies. First, should an important toxic or cancer hazard exist, large numbers of people would be at risk. The identification of such hazards is therefore important simply as a matter of public health policy. But, further, such investigations have the added advantage of being more likely to provide reliable answers as to whether or not hazards exist since, in many instances, only the experiences of large groups of people can establish their presence or absence. Indeed, if hazards of relatively low incidence are present, it might well be impossible to identify them unless we have available the experiences of a sufficiently large number of people.

Community Exposure

Industrial agents which are also widely disseminated in the community environment should be given particularly high priority. Materials such as beryllium (*5*), polychlorinated biphenyls (*6*), lead (*7*), and asbestos (*8*) come to mind, albeit not central to the production process. The fact that styrene may leach from the ever-present styrofoam cup container into its contents make this monomer a good candidate for investigation. The experiences of the industrial groups would allow us to evaluate whether or not these agents might be important for the general population and could, in addition, teach us something of the sources of environmental contamination. This recommendation is made, again, in terms of public health importance of potential human disease.

Suspect Agents

Sometimes, opportunities exist for investigations of agents in which considerations such as those above play a lesser (but not absent!) role. Where leads exist, from any of a variety of sources, it would be unwise not to follow them since there is a greater likelihood of early accomplishment with perhaps minimal allocation of resources. If there be large or moderately large numbers of people exposed, the investigation of such possibilities obviously becomes all the more important.

Thus, where agents have had biological activity already demonstrated, especially in terms of organ toxicity, the full spectrum of their potential should be explored, particularly with relation to possible carcinogenicity. We might have benefited from such a perspective with vinyl chloride (*9*), and examples could now include monomers as styrene, halogenated hydrocarbon solvents, and a number of plasticizers.

Study of chemical configuration can give additional leads, especially if experience exists suggesting that there may be generalization within classes of chemicals. At the present time, examples would be particular configurations of halogenated ethers, metabolites of known chemical carcinogens or substituted variants of such chemicals, as 3,3′-dichlorobenzidine.

Carcinogenicity in animal models is being widely discussed in relation to its basis for regulatory action and control. It would appear appropriate that it be at least equally utilized for the selection of human populations for study. The predictive value of animal carcinogenicity studies (*10, 11*) might have shortened our lag in recognition of human cancer with vinyl chloride (*12*) and bischloromethyl ether (*13*).

Not infrequently, limited data relating to human experience do not provide firm evidence for the existence of chemical toxicity or carcinogenicity. Nevertheless, such leads require appropriate extension of studies, in larger populations or with alternate epidemiological methods.

Long Use

Where agents have been in use for many decades, opportunity exists for evaluation of possible health effects; human exposure has already occurred in such circumstances for a period sufficiently long to determine whether or not disease associated with long-term, low-level exposure will occur. Even if we have no reason to necessarily suspect that hazard exists, the fact that the results of long-term human exposure are at hand, and merely have to be gathered and analyzed, provides an opportunity that deserves rather high priority. It might well be that studies of the experiences of such populations will result in demonstration that no identifiable health hazard has been associated with the exposure. This would be all to the good. It is perhaps equally important to identify agents without hazard, as those with such difficulties, from both scientific and practical points of view.

Planned Introduction or Widened Distribution of Agents

Where new chemicals are scheduled for introduction, or for greatly widened distribution, it is reasonable that their potential toxic and carcinogenic effects be questioned prior to such introduction or widened distribution. There will have to be good judgment in selection of agents, however. Where the chemical in question is unlikely to involve exposure of more than a very small number of people, in a limited operation, and if it has no resemblance to known carcinogenic chemicals and there are no hints from animal or other studies that it represents a hazard, intensive testing might be unwarranted. On the other hand, if many people are going to be exposed, and if the chemical is "suspect," its careful evaluation by all practical means would have to be undertaken.

The concept of "pretesting" is very popular at this time. It may have a different meaning, however, for the general public and for scientists. Methodological approaches are not yet fixed. I expect that much thought will be given to this problem in the next several years and that further guidelines will be established.

Methods

Toxicological and carcinogenic properties of chemical agents can be investigated in a number of ways. These are not mutually exclusive, and while the emphasis given to one or another will vary in specific cases, in general a variety of methods is likely to be useful. The selection of approaches for particular agents and the evaluation of the weight to be given to the results of each type of study will require experienced judgment.

Toxicological: Pharmacodynamics

Standard industrial toxicological study has a great deal to offer: this has become increasingly evident in the past several years. The addition of modern pharmacodynamics has steadily widened its scope.

Animal Carcinogenicity

Similarly, the authority and importance of classical animal carcinogenicity studies still remain central to any program of evaluation of the carcinogenicity of chemical agents. Recent advances in methodology and design have extended the importance of such studies (appropriate use of controls; number of species studied; lifetime observations; dose-response configurations; adequate size of exposure groups; improved facilities; alternate routes of administration).

Evaluation of Bacterial Mutagenicity Models

The use of bacterial test systems, such as that of Ames (*14*), may prove of considerable importance. At the moment, there remains considerable need for their validation in terms of animal and human carcinogenicity (*15*). It is expected that the data that will become available within the next two or three years will provide much information on this problem, as well as on its applicability to questions of interactions of multiple factors to which exposure may occur concurrently or sequentially.

Epidemiological

One of the important advances in the past decade has been the considerable progress made in epidemiological approaches to the evaluation of occupational and environmental disease. The next several years will see continued progress in this area and questions derived from epidemiological investigatians will stimulate answers from laboratory studies, and vice versa.

Experiences suggest that a variety of epidemiological approaches will be productive, and selection among them will depend upon the problems that are approached and the particular circumstances that will then obtain.

A considerable difficulty in investigation of environmental and occupational cancer has been the long period of clinical latency (*16*) between onset of exposure (or, perhaps more accurately, "effective exposure") and the subsequent clinical appearance of disease. A purely prospective approach to observation of human experience which would start at the present time is often unacceptable, simply in terms of the long time necessary to provide data that would allow appropriate judgment (*17*). (There are exceptions: occasionally, skin cancer may occur within a year or a year and a half with particularly powerful carcinogenic coal tar derivatives; sometimes, chemical-induced leukemia may also have a short induction period.)

As an alternative, it has been found that large cohorts can be identified without substantial selective bias at points of time sufficiently long in the past to allow evaluation of potential long-term toxicity and carcinogenicity. Such a method, retrospective-prospective cohort study (*3*), is particularly suitable for study of occupational and environmental hazards.

Rare or unusual tumors which might be dubbed "signal" neoplasms have been found to be of particular interest in identifying environmental carcinogens. Examples in the past have included asbestos mesothelioma (*18, 19*); angiosarcoma with thorotrast (*20*), arsenic (*21*), and vinyl chloride (*12*); nasal and sinus tumors with nickel (*22*) and among woodworkers (*23*).

To the present, there has been much insecurity concerning the reliability and applicability of morbidity studies. It is likely that, with appropriate care and design, much better use can be made of the vast amount of data available in such records. Methodological advances are needed, but these are in the offing.

The classic approach of case-control comparison studies has also been found useful in investigation of environmental cancer (*24*), and it may be that much more extensive use will be made of this method, particularly in industrial circumstances, since the "control cases" can be suitably matched to the index cases in all respects other than exposure to the suspect agent. It may even be possible to utilize matched-pair analysis if sufficient large populations are available and if environments can be sufficiently well characterized. This has proven a highly successful method for isolating particular influences from amidst confusing variables (*25, 26*).

Epidemiological methods needed for investigation of community effects of occupational agents are now being developed and such focused community studies show great promise. Clear attention was first called to the potential of such investigations by the neighborhood cases of beryllium disease at the end of the 1940's (*5*) and emphasized by the neighborhood mesotheliomas with asbestos exposure during the 1960's (*24, 27*). Neighborhood populations can be well defined and separated from the general community. Their experiences will give much information concernig the effects of "low-level" environmental exposure. Further, recent epidemiological experiences indicate that family contact (conjugal) investigations can be quantitatively designed to provide information not merely to show that conjugal disease is possible [which we have known since 1936, with the report of PCB chloracne among family contacts (*6*)], but that the level of risk can be established and information concerning dose-disease response relationships of the agent in question can be obtained.

Cancer registries have, to the present, made but limited contributions to the evaluation of occupational and environmental disease. The utilization of coordinated registry-based data is being reviewed, however, and it is likely that much better use of their potential will be found in the future.

Finally, it is likely that there will be much study of the effects of chemical agents in terms of mutagenicity and teratogenicity and that the relation to potential carcinogenicity will be evaluated. At the present time, the significance of the teratogenic potential of a chemical agent to a risk of carcinogenicity has not been clearly established. It is likely that this will be a fruitful area for investigation in the future, both in laboratory and epidemiological terms. Birth defect registries may have an important role to play here. Interaction with focused community studies (see above) is also likely to occur.

Multiple Factor Interactions

The recent identification of multiple factor interactions in the etiology of human cancer has placed increased emphasis on previous information from laboratory studies (*28*). Hammond and I consider that investigation of multiple factor interactions should now represent a major perspective in the study of environmental causes of human cancer (*29, 39*). This is likely to be particularly true in the plastics and synthetic rubber industry, where exposure to a single agent is the exception rather than the rule. This understanding should be a background to both epidemiological and laboratory approaches. It has implications, too, in terms of prophylaxis, and control. Sometimes, agents involved will be able to be clearly defined, as the influence of cigarette smoking in the incidence of lung cancer among asbestos-exposed workers (*29*); at other times, it may be difficult to decide what the factors are, as with the decrease in the cancer risk among nickel smelter workers in South Wales, following the modification of smelting processes in 1925 (*31*).

Industry Opportunities

Industry has both special responsibilities and special opportunities in the area of environmental disease and, particularly, environmental cancer.

Epidemiological

One of the most difficult problems in evaluating potential toxicity and/or carcinogenicity of occupational and environmental agents is the fact that identifiable exposed populations are often too small to allow for statistically reliable analysis. This is particularly true when the effects being considered have long periods of clinical latency and the populations at risk which meet the requirements of a long period from first exposure are particularly small. It is possible to circumvent this difficulty by coalescence of a number of groups exposed to the same agent, as by combining exposed populations in a number of plants in the same industry, providing industry-wide cohorts. Sometimes, this can be accomplished by the use of union records. In other instances, cooperation among a number of companies can provide the same opportunity. We have already seen that this can be accomplished in the plastics and rubber industries, and we look forward to the reports of the research groups at the University of North Carolina and the Harvard School of Public Health (*32*).

Industry records are likely to be particularly valuable in another area, that of exposure of maintenance personnel. As matters now stand, chemical operators are sometimes least exposed to high concentrations of toxic chemical agents. Rather, maintenance personnel, accustomed to dealing with leaks, breakdowns, clean-outs, etc., may be more likely to have excessive exposure. Such individuals are sometime not included in studies of "chemical workers" since they are often separately categorized as steam-fitters, carpenters, electricians, welders, etc. Their identification in industry records would provide a much more exact categorization of potential exposure and facilitate evaluation of their experience.

In an analogous problem, analysis of the total plant population carries the risk of a dilution effect. Hazard may be associated with one intermediate chemical among workers employed at a single point in the process. Knowledge of the total process, available to industrial management, allows for appropriate categorization of exposures and associated hazard. Indeed, this concept—vertical analysis of agent use—can extend to delivery and use of raw materials, and the finished product, as well. The episode of Epping jaundice provides a good example (*33*). Sometimes very valuable information can be obtained concerning the risk of toxic effects by noting changes in incidence and kind of reaction, over periods of time associated with changes in the production process. The nickel (South Wales) episode has been commented on. Too, the effect of changes in exposure levels might also be studied.

A particularly valuable opportunity for industry lies in its ability to identify those individuals who constituted initial exposed groups. It not infrequently happens that agents are introduced into production and into commerce with no hint of potential toxicity or carcinogenicity. Questions in this regard can first be raised decades later. In such instances, it would be particularly valuable to know the long-term experience of those people first exposed to the agent in question. Industry records would be unique.

The foregoing implies some reorientation of industry record keeping practices. Employment records in industry are designed for specific purposes and, within these perspectives, are kept for varying periods of time. It will be necessary in the future to consider the use of these record systems in a somewhat altered form, to include data that will be valuable later in occupational health terms, and kept for much longer periods of time. Fortunately, computerization of records allows this to be done.

Environmental Surveillance

It is unlikely that governmental control and surveillance agencies such as the Occupational Safety and Health Administration of the Department of Labor will be able to undertake large-scale, long-term serial environmental measurements in industry and it is uncertain whether such agencies should properly do this on a continuing basis. Industrial management is much more familiar with the details of their production processes and may be considered, moreover, to have a special responsibility for the evaluation of chemical exposures associated with them. Still, the extent and range of environmental measurements is potentially immense and probably not possible with current industrial hygiene resources. Therefore, thought should be given by industry to the automation of environmental measurements.

This is much more than an engineering problem, however. Just as with epidomiological studies, the collection of masses of data, inadequately focused, may present more problems than are resolved. It would be well, therefore, to look to close collaboration between biological and engineering scientists, for the design of environmental surveillance. What we measure will be at least as important as how we measure.

Medical Surveillance

There is a long tradition of industry participation in the medical surveillance of its employees. I suggest that it is possible to extend this ongoing system for the detention of toxic and carcinogenic agents in the industrial environment. It would be a matter of little added expense or difficulty to extend currently adopted examination procedures to include toxicological surveillance, since these would necessitate, generally, only additional biochemical studies, possible cytological investigations and x-rays of specific sites (lung). Where particular hazards are identified, further additions would be warranted (x-rays of hands with vinyl chloride exposure, for example). Again, because large numbers of examinations would be required, periodically, it is likely that emphasis will be given to automation of examination procedures.

A special problem is that of confidentiality. Although statistical results of studies should be available to industry and labor, I suggest that information concerning individuals should be entirely confidential; there should be (and often is, nowadays) clear separation of the responsibilities of the medical departments and the personnel departments of companies in the rubber and plastics industries.

Further Perspectives

Backlog of Unstudied Problems

Starting shortly before the last World War, continuing through it and in the period since, there has been vast extension of the chemical industry. One need but point to the remarkable growth of the plastics industry to appreciate this (0.1 million tons produced in 1930; 30 million tons in 1970). Comparatively little study of the toxic effects of many of the agents involved, particularly those observable only after long periods of maturation, was undertaken until the past 5–10 years. Simultaneously, it is necessary to investigate and define toxicity problems associated with current use and current agents.

Industry-Labor Cooperation

The growing concern and sophistication of labor groups with problems of occupational health and the increasing awareness of such problems in industry sharply raise the question of how these concurrent perspectives can be meshed. In the past, it was sometimes considered that the interests of each group was opposed to that of the other, apparently because of the knowledge that industrial health leads to considerable added cost. Such assumptions should no longer be automatically made. Rather, it is in the interest of all concerned to consider and develop close cooperation between industry and labor groups in investigating problems of toxic potential of industrial agents. Both should be involved in the process of considering and identifying potential problems, planning and management of the research programs, and analysis of the results. This is no longer the prerogative of one or the other, and neither will necessarily be satisfied merely with receiving the conclusions at the end of a study.

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